REMARKS/ARGUMENTS

This Response is being submitted in response to the Office Action dated April 16, 2008. Claims 6, 13, 16, 18, 21, and 23 were previously cancelled, claims 2-5, 7-12, 14-15, 19-20, 22, and 26 were previously amended, claims 17, 25 and 26 are currently amended, and claims 1, and 24 are original. Claims 1-5, 7-12, 14-15, 17, 19-20, 22, and 24-26 are and remain pending in this application and claims 1-5, 7-12, 14-15, 17, 19-20, 22, and 24-26 stand rejected. Reconsideration and reexamination are respectfully requested.

Specification

The Examiner objected to the abstract and the specification as allegedly being unclear. Applicant has amended the specification and the abstract and submits that the specification and the application conform to applicable requirements. Applicant respectfully requests withdrawal of these objections.

Claims

The Examiner objected to Claim 17 on the grounds of a misspelling. Applicant submits that the correct spelling appears in the amended claim 17 and requests reconsideration and withdrawal of the objection hereto.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 25 and 26 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. These claims have been amended and conform to applicable requirements for definiteness under 35 U.S.C. § 112, second paragraph. Applicant respectfully requests reconsideration and withdrawal of these rejections.

Rejections Under 35 U.S.C. § 103

Claims 1-5, 7-12, 24, and 26 stand rejected under 35 USC 103(a) as purportedly being unpatentable over Cassel (US 2002/0128285, hereinafter "Cassel"), and, separately, that Claims 1-5, 7-9, 19-20, 22, 24, and 26 are rejected under 35 USC 103(a) as purportedly being unpatentable over Samuels et al. (US 2002/0006435 A1, hereinafter "Samuels"). The Examiner has further rejected Claims 14-15 as purportedly unpatentable over Cassel in view of Lutz et al. (US 5,750,139, hereinafter "Lutz"), Claim 17 as purportedly unpatentable over Cassel in vies of Santana et al. (US 2003/0103955 A1, hereinafter "Santana"), and Claim 25 as purportedly unpatentable over Cassel and Samuels in view of Lutz and Santana.

Applicant respectfully disagrees with the allegation that Applicant's development would be obvious to one skilled in the art for the following reasons, inter alia.

In summary, the presently claimed combination provides unpredictable purposes and unpredictable results, and is thus NOT a mere substitution or addition for a known purpose, nor yielding predictable results. Therfore, and per the Supreme Court case of KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385 (2007), the present claims are thus patentable over the cited art.

Even so, and as a preliminary matter, Applicant will provide here some background and context with respect to the present developments.

Applicant's specification describes in detail the priorly existing, state-of-the-art EMLA composition, the prilocaine-lidocaine cream, its constituents, and the adverse effects associated therewith. Prilocaine has adverse side effects of methemoglobinaemia and cyanosis. Lidocaine is the most commonly used local anesthetic; however, unfortunately, when administered topically, lidocaine is not effectively absorbed transdermally, but only through mucosal surfaces.

According to paragraph [0010] of the present specification, an important inconvenience of EMLA is that its onset time for anesthesia is relatively long,

approximately one hour or more. This onset time is not very practical for several clinical procedures. For more invasive procedures such as split skin graft harvesting, EMLA has to be applied at least two hours prior to surgical operation. Such delay is a problem for both patients and for medical staff, particularly in the area of pediatrics. Moreover, EMLA is formulated at pH 9.0 to incorporate the anesthetic agents in base form. The skin, which has an acidic pH (5 to about 5.5) is sensitive to such a high basic pH and significant skin irritation can occur. Dermal application of EMLA may cause a transient, local blanching followed by a transient, local redness or erythema. Another disadvantage of EMLA is that for deep penetrative effect it is necessary that the cream is applied under occlusive dressing.

In view hereof Applicant has achieved an improved topical anesthetic composition overcoming one or more of these adverse side effects. As a basis of these developments, Applicant has developed a topical anesthetic with the benefits of lidocaine and prilocaine, but free of one or more of the limitations associated therewith (Bouffard Fita, para. [0013]).

Applicant's developments include specific combinations of anesthetics: lidocaine, prilocaine and tetracaine. The new and different, hitherto unpredictable advantages, purposes and effects of such compositions include, inter alia, one or more of:

a) Removing the need for an occlusion to achieve the anesthetic effect (EMLA protocol specifies that occlusion is compulsory);
b) Decreasing side effects observed because the amount of prilocaine is reduced (the main cause of side effects);
c) Speeding the anesthetic effect which appears after a brief period (about 20 minutes) whereas this effect using an EMLA composition appears after a longer period (as indicated in the background section);
d) Lengthening the anesthetic effect which lasts about 3-4 hours whereas the anesthetic effect of the EMLA composition lasts a shorter period of time;
e) Stabilizing tetracaine. It is well-known in the state of the art that tetracaine is not stable, decreasing its bioavailability and, therefore, decreasing its anesthetic

effect. Surprisingly, the presence of prilocaine compensates for the degradation of tetracaine and, therefore, it has a good bioavailability and a correspondingly good anesthetic effect.

These advantages of the presently claimed formulations are fully supported by the experimental data included in the present specification. Tables 1-3 of Applicant's specification illustrate that Applicant's compositions show a greater efficacy and a shorter time of effect establishment versus EMLA for the same type of dermatological and/or dermoesthetic procedure. The effectiveness of EMLA is practically half with a doubled time of application.

These are directly the kinds of unpredictable purposes and/or effects which support patentability under KSR, inter alia.

Prior art cited by the examiner

Cassel

Claims 1-5, 7-12, 24, and 26, and particularly claim 1, have been rejected by the Office Action statement, inter alia, that Cassel teaches "topical delivery of a local anaesthetic" and that "the preferred local anaesthetics include lidocaine, prilocaine, and tetracaine" and further that "it would have been obvious to one ordinary skill in the art at the time of the invention" to combine the lidocaine/prilocaine composition with the lidocaine/tetracaine composition as taught by Cassel. Office Action of April 16, 2008, pages 6-7. The claims, particularly claim 1, have also been rejected by the Office Action statement that it would be obvious to one skilled in the art to determine the optimal or workable amount of the Applicant's components, which are not found in Cassel, by routine experimentation. Office Action of April 16, 2008, page 7.

More particularly, the Office Action alleges that:

However, it would have been obvious to one of ordinary skill in the art at the time of the invention, to combine the lidocaine/prilocaine composition with the

> *lidocaine/tetracaine composition as taught by Cassel, to form a third composition comprising all three anesthetic agents. One of ordinary skill in the art would have been motivated to do so because both prior art compositions have utility as topical anesthetic compositions, and the combination of the compositions is claimed to have utility as topical anesthetic composition. It is obvious to combine individual compositions taught to have the same utility to form a new composition* ***for the very same purpose****. (Office Action of April 16, 2008, page 7, para. 1; emphasis added here).*

However, as introduced above, and described further below; Applicant's composition provides one or more new and different, unpredictable purposes, not the "same purpose."

What Cassel teaches, on the other hand, is that in order to improve the effectiveness and tolerance of the present topically effective therapy, local anesthetics with different pharmacodynamics and pharmacokinetics may be combined in a pharmaceutically acceptable topical drug formulation. A first Cassel-preferred combination of local anesthetics was lidocaine and prilocaine and a second Cassel-preferred combination was lidocaine and tetracaine (Cassel, para. [0030]). Paragraphs [0057] and [0058] describe that when a combination of local anesthetics is used, the preferred combination is an eutectic mixture of lidocaine and prilocaine or of lidocaine and tetracaine. The ranges of amounts of each component in such mixtures are also described.

At the time of the Cassel developments, these two two-component combinations were well known. The first combination lidocaine/prilocaine was sold as EMLA and the second lidocaine/tetracaine was known as AMLI cream. Cassel does not teach anything more than the prior existence of these two commercial formulations and his adoption for use in his process. More particularly again, Cassel refers only to the fact of known anesthetics that can be topically locally applied to treat the pain associated with a surgically closed wound.

Moreover, as an appreciated fact, these combinations of two anesthetic agents and other further options of combinations are/were described in detail in the Background of section of Applicant's' presently-in-issue specification as being well-known in the art and therefore, providing the basis upon which Applicant's developments were made. Some other known approaches involved the combination of topical anesthetics with a vasoconstrictor (see Samuels discussion below); the combination of several anesthetic agents and different topical excipients (e.g. EP 43.738-A, WO 9633706-A); and the lidocaine-prilocaine cream named EMLA (US Pat. No. 4,562,060) (Bouffard Fita, para. [0009]). As set forth in detail, EMLA presents some adverse effects, so in Applicant's' Background section it is disclosed that there have been several attempts trying to improve EMLA cream (including provision of a vasodilator, or a lipophilic base) (see Bouffard Fita specification, para. [0011]).

Cassel selects two preferred combinations of pairs of anesthetics. Cassel does not go beyond citing these two preferred combinations (lidocaine/prilocaine and lidocaine/tetracaine). This knowledge was completely appreciated and known in the art, and therefore described in Applicant's' Background section. Applicant is going beyond this knowledge to get a further, hitherto unknown composition with very specifically desired, different, new and unpredictable properties.

Therefore, Applicant respectfully does not agree that it would have been obvious to one of ordinary skill in the art at the time of the invention, to combine the separate Cassel compositions, i.e., the lidocaine/prilocaine composition with the lidocaine/tetracaine composition, to form a third composition comprising all three anesthetic agents. By maintaining them separately, Cassel did not teach their combination. Furthermore, Applicant does not agree that one of ordinary skill in the art would have a motivation to combine them either. Cassel found each separately effective for his intended purpose, limited as it was, and thus did not suggest going further. It is not obvious to combine two combinations of two anesthetics to get one of three anesthetics if there is no objective to do so, and no such objective was given.

Note, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." In re Kahn, 441 F. 3d 977, 988 (Fed. Cir. 2006). The law of obviousness requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385 (2007) (note, KSR left fully in tact the teaching, suggestion or motivation test); See also, e.g., MPEP 2143, inter alia; see also In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (concentrating upon what prior art actually 'taught', 'expressed', 'conveyed', and/or 'spoke of').

Merely combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385 (2007); and see, United States v. Adams, 383 U.S. 39,42-43, 51-52, 148 USPQ 479, 480, 483-84 (1966) (stating that "[d]espite the fact that each of the elements . . . was well known in the prior art, to combine them as did Adams required that a person reasonably skilled in the prior art must ignore the teaching away of the prior art . . . ."). "When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious." KSR v. Teleflex, supra, at 1395.

The Office Action alleges that one skilled in the art would have been motivated to make the present combination because each of the prior art compositions have separate, discrete utilities as topical anesthetic compositions, and the alleged combination of those prior compositions would then apparently also have utility as a topical anesthetic composition. The Office Action also alleges that it is obvious to combine individual compositions taught to have the same utility to form a new composition for the same purpose. While in this sense, it may be true that both prior art compositions have separate utilities as topical anesthetic compositions, there nevertheless is neither teaching in Cassel nor motivation therefrom to combine both

compositions to get a new composition, particularly not a new composition with the unpredictable different and new purposes, effects and utilities of the presently-claimed new compositions; the purposes/effects namely being, the removal of the previously compulsory occlusion; the reduction in side effects; the speeding of the anesthetic effect; the lengthening of the anesthetic effect; and the increase in tetracaine stability, bioavailability and, therefore, anesthetic effect, due to the presence of prilocaine. No such prior utilities, purposes or effects existed and thus no such motivation exists to create them.

Thus, what is provided here is not a mere substitution or even addition of parts for the same purpose, but rather an addition to achieve one or more additional purposes hitherto unknown nor predicted. KSR said substitution for the same purpose may not be patentable; however, here we have addition for one or more different purposes, heretofore unpredicted.

In Cassel a different problem is solved, thus the motivation from Cassel is in a different direction. One skilled in the art would have not been motivated to take the above steps because the Applicant's problem to be solved is a problem other than Cassel's provision of "a composition with utility as topical anesthetic composition" as alleged by the Examiner. The problem to be solved in Cassel is not providing a new topical anesthetic composition, particularly not one with different effects like removal of the occlusion, reduction in side effects, speeding and lengthening anaesthetic effect and/or stabilizing tetracaine. Conversely, the Applicant has provided a topical anesthetic composition that overcomes the problems of EMLA and others. Cassel certainly does not teach that modifying the composition adding a new component would result in any improvement in any aspect. In Cassel, combinations of two anesthetics are mentioned, but it is certainly not indicated that by adding a component an improvement could be achieved, particularly not any unpredictable effect or purpose.

In the subject Application, an improved and different effect is achieved with the combination of the three anesthetics: tetracaine, lidocaine and prilocaine are selected.

When adding the third component to the two anesthetics composition, there are surprising new and different effects in the final composition.

(i) Starting from the lidocaine/prilocaine combination disclosed in Cassel, the addition of tetracaine is not obvious.

In Applicant's specification, the lidocaine/prilocaine combination disclosed in Cassel is referred to as EMLA. Throughout Applicant's specification the side effects of this composition are described (e.g., in the "Background" section).

As disclosed in the Applicant's application, tetracaine is an added component over and above the lidocaine+prilocaine composition.

In Applicant's "Examples" section, comparative assays are included and illustrate the different effect of the EMLA composition and Applicant's composition. The fact of adding the tetracaine to the EMLA composition gives rise to the following unpredicted advantages over EMLA:

a) There is no need for an occlusion to achieve the anesthetic effect (EMLA protocol specifies that occlusion is compulsory);
b) A decrease in the side effects is observed since the amount of prilocaine is reduced (the main cause of side effects);
c) The anesthetic effect appears after a brief period (about 20 minutes) whereas this effect using an EMLA composition appears after a longer period (as indicated in the background section);
d) The anesthetic effect lasts about 3-4 hours whereas EMLA composition lasts for a shorter period of time.

The advantages of Applicant's formulation have been referenced in para. [0026-0027] of the specification. These advantages are fully supported by experimental data included in the application. Tables 1-3 illustrate that Applicant's' composition proves a larger efficacy and a shorter time of effect establishment versus EMLA for the same

type of dermatological and/or dermoesthetic procedure. The effectiveness of EMLA is practically the half with a double time of application.

These new effects are not suggested as desired by Cassel, nor are they suggested as predictable from Cassel, thus, no motivation comes from Cassel toward their achievement.

(ii) Starting from the lidocaine/tetracaine combination disclosed in Cassel, the addition of prilocaine is also not obvious.

It is well-known in the art that tetracaine is not stable, resulting in decreased bioavailability and, therefore, decreased anesthetic effect. On the other hand, as pointed out in the Background section of Applicant's specification the use of prilocaine as an anesthetic gives rise to important side effects. Cassel does not address the stability problem or any direction toward its solution. Thus, Cassel does not motivate adding prilocaine to stabilize the tetracaine.

Surprisingly and thus unpredictably, the addition of prilocaine to the lidocaine/tetracaine composition compensates for the degradation of tetracaine and, therefore, results in good bioavailability having the desired anesthetic effect. Furthermore, nearly none of the side effects associated with prilocaine are observed. Thus, the claimed invention yields unexpectedly improved properties or properties not present in the prior art, i.e., unexpected and unpredictable properties. *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990). This showing of unexpected results is based on evidence presented in the specification. *In re Mayne*, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997)

This situation is not one of simple substitution, nor is it one of a simple 'upgrade'. See, cf., KSR, supra at ___, 82 USPQ2d at 1399 (discussing 'upgrading Asano with a sensor.') Applicants' presently claimed developments involve far more than a simple addition, combination, replacement, or upgrade. The innovations in Applicants' claims

include, at least in part, the careful combination of potentially problematic local anesthetics and a mastery of the optimal balance of each to achieve the desired new and different effects. Simply adding the cited elements of Cassel on top of each other would not be predicted to achieve the present new and different results and would fail to achieve Applicants' end results. Modifications far beyond those merely taught by Cassel would be required to enable a compound of the type claimed by Applicant here. Given the known side effects that characterize prilocaine (which are specifically mentioned in Applicant's application), one skilled in the art would not have selected this compound as a way to add to a successful and existing anesthetic formulation. Contrarily, the side effects of prilocaine would teach away from adding prilocaine into the composition, i.e., taking a known anesthetic combination lidocaine/tetracaine with its own problems (instability, etc.), would not suggest adding a further anesthetic with its own alternative problems (known side effects) to achieve a better product. The known side effects would alone suggest not adding prilocaine.

From the points set out above, the obviousness rejection on Cassel is obviated and/or traversed at least on the grounds that:

- the Applicant's development was not predictable;
- the Applicant's development showed no reasonable expectation of success;
- there were not a "finite number of identified, predictable solutions";
- Applicant's development showed unexpected results;
- Cassel teaches away from the solution offered by Applicant.

Thus, Applicant's Claim 1 is not obvious from Cassel. Moreover, Applicant respectfully submits that Applicant's dependent claims 2-5, 7-12, and 24, are allowable at least, for the same reasons set forth above in that they contain the combination of elements of claim 1 which are not properly taught or suggested by Cassel. Claim 26 is likewise patentable over Cassel. Reconsideration and withdrawal of these rejections are thus also respectfully requested.

Samuels

Claims 1-5, 7-9, 19-20, 22, 24, and 26, and particularly claim 1, stand rejected on the allegation, inter alia, that Samuels teaches "compositions for topical application comprising a therapeutically effective amount of topical anesthetic" and that "preferred agents include lidocaine, prilocaine, and tetracaine" and further that "it would have been obvious to one ordinary skill in the art at the time of the invention" to combine the lidocaine/prilocaine composition with the lidocaine/tetracaine composition as taught by Samuels. Office Action of April 16, 2008, page 8. The rejection further alleges that it would be obvious to one skilled in the art to determine the optimal or workable amount of the Applicant's components, which are not found in Samuels, and to add a viscosity increasing agent, by routine experimentation. Office Action of April 16, 2008, page 7.

The Office Action alleges that:

> *However, it would have been obvious to one of ordinary skill in the art at the time of the invention, to combine the lidocaine/prilocaine composition with the lidocaine/tetracaine composition as taught by Samuels, to form a third composition comprising all three anesthetic agents. One of ordinary skill in the art would have been motivated to do so because both prior art compositions have utility as topical anesthetic compositions, and the combination of the compositions is claimed to have utility as topical anesthetic composition. It is obvious to combine individual compositions taught to have the same utility to form a new* ***composition for the very same purpose****. (Office Action of April 16, 2008, page 9, para. 3; emphasis added here)*

However, as introduced above, and described further below; Applicant's composition provides one or more new and different, unpredictable purposes, not the "same purpose."

Moreover, and contrary to this allegation, Samuels teaches compositions for topical application comprising a therapeutically effective amount of topical anesthetic, a pharmaceutically acceptable carrier, but also a therapeutically safe and effective amount of at least one topical vasodilator (Samuels, para. [0011-0014] and claims).

Samuels starts from the use of lidocaine as a topical local anesthetic and from the use of EMLA composition (lidocaine/prilocaine). Samuels et al. states that

prolongation of anesthesia has been achieved in the art by the addition of vasoconstrictors (Samuels, para. [0006]). From that point, the Samuels' combination (and teaching) is that by incorporating a vasodilator into a composition comprising transdermal anesthetics in a pharmaceutically acceptable carrier, a transdermal formulation is produced which has both anesthetic and vasodilator properties (Samuels para. [0009-0010]).

In Samuels, the combination is applicable to any topical anesthetic, especially those with vasoconstrictive properties. Many examples are listed and it is mentioned that the anesthetics may be used individually or in mixtures ([0034]). Samuels discloses that preferably, the anesthetic agent comprises an eutectic mixture of lidocaine and prilocaine. In another embodiment, the topical anesthetic is an eutectic mixture of lidocaine, prilocaine and dibucaine (Samuels, para. [0035, 0039], claim 6). The mixture can be also of lidocaine and tetracaine hydrochloride (Samuels, Example 6).

Applicant respectfully disagrees with the respective Office Action allegations that: "it would have been obvious to one of ordinary skill in the art at the time of the invention, to combine the lidocaine/prilocaine composition with the lidocaine/tetracaine composition as taught by Samuels, to form a third composition comprising all three anesthetic agents."; or that "One of ordinary skill in the art would have been motivated to do so because both prior art compositions have utility as topical anesthetic compositions, and the combination of the compositions is claimed to have utility as topical anesthetic composition."; or that "It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose". (Office Action of April 16, 2008, page 9, para. 3.)

The reasons are substantially the same as those argued above with respect to Cassel: in Samuels, a different problem is solved, and the composition here is set forth not for the same purpose, but, for the accomplishment of one or more of multiple different and new, as-yet unpredicted purposes. The skilled in the art would have not been motivated because the problem(s) to be solved by Applicant is(are) different

one(s) from the mere providing of "a composition with utility as topical anesthetic composition". Applicant's problem to be solved is/was not merely providing another topical anesthetic composition. Rather, the problem to be solved is/was to provide a topical anesthetic composition that overcomes the problems of EMLA and others. Samuels certainly does not teach that modifying the composition by adding a new anaesthetic component would result in any improvement in any aspect. In Samuels, combinations of two and three anesthetics are mentioned, but there is not any indication that by adding a further anasthetic component any improvement is achieved.

The problem to be solved in Samuels was to achieve a prolongation of anesthesia by the incorporation of a non-anasthetic component, particularly there, a vasodilator, into the composition including transdermal anesthetics and a carrier. As noted below, this Samuels direction actually teaches away from addition of a third anaesthetic; Samuels is teaching a vasodilator to lengthen effect, hence giving up on the field of anasthetics alone to lengthen effective time. Samuels in effect teaches others that if they want longer activity they need to go to a very different kind of additive, the vasodilator, teaching away from adding a third anaesthetic.

Therefore, there is no motivation neither teaching derived from Samuels to combine the two combinations lidocaine/prilocaine and lidocaine/tetracaine in order to get the new three-component composition of Applicant with the new and different and as-yet unpredictable results here achieved. The composition of Applicant is another very different and independent solution to the different problem of improving properties of anesthetic compositions.

Applicant's improved effect is achieved with the combination of the three anesthetics tetracaine, lidocaine and prilocaine. When adding the third component to the two anesthetics composition, there are surprising as-yet unpredictable effects in the final composition.

(i) Starting from the lidocaine/prilocaine combination disclosed in Samuels, the addition of tetracaine is not obvious.

The lidocaine/prilocaine combination disclosed in Samuels is/was known as EMLA. Throughout Applicant's specification the side effects of this composition are described (e.g., the "Background" section). Tetracaine is an additional component over and above the prior lidocaine+prilocaine composition.

In Applicant's "Examples" section comparative assays are included and illustrate the different effect of the EMLA composition and Applicant's composition. Adding the tetracaine to the EMLA composition gives rise to the following unpredictable advantages:

a) No occlusion is needed to achieve the anesthetic effect (EMLA protocol specifies that occlusion is compulsory);
b) A decrease in the side effects is observed since the amount of prilocaine is reduced (the main cause of side effects);
c) The anesthetic effect appears after a brief period (about 20 minutes) whereas this effect using an EMLA composition appears after a longer period (as indicated in background section).
d) The anesthetic effect lasts about 3-4 hours whereas the effects of the EMLA composition last a shorter period of time.

The advantages of Applicant's formulation have been referenced in para. [0026-0027]. These advantages are fully supported by experimental data included in the application. Tables 1-3 illustrate that Applicant's composition has a greater efficacy and a shorter time of effect establishment versus EMLA for the same type of dermatological and/or dermoesthetic procedure. The effectiveness of EMLA is practically half with a doubled time of application.

These new effects are not suggested as desired by Samuels, nor are they suggested as predictable from Samuels, thus, no motivation comes from Samuels toward their achievement.

(ii) Starting from the lidocaine/tetracaine combination disclosed in Samuels, the addition of prilocaine is also not obvious.

It is well-known in the art that tetracaine is not stable, decreasing its bioavailability and, therefore, decreasing its anesthetic effect. On the other hand, as it is pointed out in Applicant's Background section, the use of prilocaine as an anesthetic gives rise to important side effects. Samuels does not address the stability problem or any direction toward its solution. Thus, Samuels does not motivate adding prilocaine to stabilize the tetracaine.

Surprisingly and thus unpredictably, the addition of prilocaine to the lidocaine/tetracaine composition compensates the degradation of tetracaine and, therefore, it has a good bioavailability having the desired anesthetic effect. Furthermore, nearly no side effects associated to prilocaine are observed.

Given the known side effects which characterized prilocaine (which are specifically mentioned in Applicant's specification), one skilled in the art would not have selected this compound to prepare, i.e., add to the anesthetic formulation. Rather, the side effects of prilocaine would instead teach away the skilled in the art from adding prilocaine into the composition. Moreover, the teaching of addition of a very different kind of effective agent, the vasodilator, for a particular effect, lengthening effective period, teaches away from adding a further anesthetic for the same of a similar purpose.

Thus, Applicant's claim 1 is not obvious from Samuels. Moreover, Applicant submits that Applicant's dependent claims 2-5, 7-9, 19-20, 22, and 24, are allowable at least, for the same reasons set forth above in that they contain the elements of claim 1 not properly taught or suggested by Samuels. Claim 26 is likewise patentable over

Samuels. Reconsideration and withdrawal of these rejections are thus also respectfully requested.

Cassel and Lutz

_____First of all, Lutz does not cure the lacking of Cassel in not disclosing or suggesting the combination of all three anasthetics herein issue. Thus, no combination of Cassel with Lutz will result in any of the claimed compositions and thus, such combination Cassel with Lutz fails to render obvious Applicant's independent and dependent claims having such elements. Claim 14 and 15 are thus patentable over Cassel in view of Lutz.

Moreover, the Office Action recognizes that Cassel does not teach dimethyl sulfoxide nor its amounts present in the composition as a penetration enhancer as presently claimed in Claims 14-15.

As a further matter, Lutz is directed to benzopyrone and the dermal application thereof. Benzopyrone is used for venous, vascular diseases, protein-rich edemas, and protein-rich lymphedemas, particularly for chronic venous insufficiency, phlebitis, and cancers. This is non-analogous art to that practiced by Applicant and described in Applicant's specification.

Furthermore, both Cassel and Lutz are complete inventions in and of themselves. The skilled artisan in Cassel would not look to Lutz to solve a problem already solved by Cassel, and vice-versa.

As explained above, the amount of experimentation necessary to reach the desired amounts would be beyond that undertaken in either Cassel or Lutz. This further illustrates the nonobviousness in Applicant's development.

Additionally, Lutz requires at least one neutral or carboxylic acid-based active ingredient, which Applicant does not. Finally, Lutz mentions in passing that DMSO and N-methylpyrrolidone can be used as a solvent. As conceded in the Office Action, Lutz does not teach any amounts.

Thus, claims 14-15 are not obvious on any combination of Cassel and Lutz.

Cassel and Santana

_____First of all, Santana does not cure the lacking of Cassel in not disclosing or suggesting the combination of all three anasthetics herein issue. Thus, no combination of Cassel with Santana will result in any of the claimed compositions and thus, such combination Cassel with Santana fails to render obvious Applicant's independent and dependent claims having such elements. Claim 17 is thus patentable over Cassel in view of Santana.

Moreover, the Office Action recognizes that Cassel does not teach hyaluronidases or derivatives of mucopolysaccharides as a spreading agent as presently claimed in Claim 17.

As a further matter, Santana does not teach mucopolysaccharides in general, as does Applicant, but is instead limited to hyaluronidases. Furthermore, Santana teaches hyaluronidase as part of a specific three-element composition of diclofenac. Diclofenac has an anti-inflammatory effect and is used, i.e., to treat arthritis. This is non-analogous art to that practiced by Applicant and described in Applicant's specification.

Furthermore, both Santana and Cassel are complete inventions in and of themselves. The skilled artisan in Cassel would not look to Santana to solve problem already solved by Cassel, and vice-versa.

As explained above, the amount of experimentation necessary to reach the desired amounts would be beyond that undertaken in either Cassel or Santana. This further illustrates the nonobviousness in Applicant's development.

Finally, Applicant's situation is not analogous to simply 'reading a list and selecting a known compound to meet known requirements'. Applicant conducted experimentation and balancing to determine proper amounts despite indications to the contrary set forth in the prior art. Therefore, Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327 (1945), is inapposite. The situation here has little to do with simply fitting the last piece into a jigsaw puzzle. There are no 'pieces' provided by Cassel and Santana, the latter of which fails to teach the mucopolysaccharidases discussed in

Claim 17. The situation would be more analogous to someone having to machine their own jigsaw puzzle piece, which is far beyond the principles of Sinclair & Carroll, supra,.

Cassel, Samuels, Lutz, Santana

First of all, neither Lutz nor Santana cure the respective lackings of Cassel and Samuels in not disclosing or suggesting the combination of all three anasthetics herein issue. Thus, no combination of Cassel and/or Samuels with either Lutz and/or Santana will result in any of the claimed compositions and thus, all such combinations, Cassel and/or Samuels with either Lutz and/or Santana, fail to render obvious Applicant's independent and dependent claims having such elements. Claim 25 is thus patentable over these combinations of citations..

The Office Action includes the admission that neither Cassel nor Samuels nor Lutz nor Santana teach a composition containing all the specific components and their weight percentages as claimed in Claim 25.

As pointed out above on the issue of nonanalogous art, one skilled in the art would not look to combine all four references to solve problem already solved by each individual invention, particularly not when the problem(s) solved are different herefrom.

Additionally, to determine the very specific amounts taught by Applicant's Claim 26, undue experimentation would be needed to determine such specifically claimed amounts, as discussed above. This is far more effort than simply selecting an ingredient off a list, as was the case in Sinclair & Carroll, supra.

The presumption of obviousness will be rebutted if it can be shown: (1) That the prior art taught away from the claimed invention, In re Geisler, 116 F.3d 1465, 1471 (Fed. Cir. 1997); or (2) that there are new and unexpected results relative to the prior art, In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990).

Here, Applicant has demonstrated that the particular range can provide desirable, yet unpredictable and thus new and unexpected results, generally by

showing that the claimed range achieved different purposes and effects over that which was available with the prior art range. *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934. Furthermore, as discussed above, the combination of lidocaine, prilocaine, and tetracaine yields unexpected and advantageous results from which the prior art taught away. Accordingly, the optimization of variables by Applicant is nonobvious.

As a final matter, an Examiner taking "official notice" of the basic knowledge or common sense of a person of ordinary skill in the art to supplement the specific teachings of the art, must provide some form of evidence in the record to support such an assertion of common knowledge. In re Zurko, 258 F.3d 1379, 1386, 59 U.S.P.Q.2d1693, 1697 (holding that general conclusions concerning what is "basic knowledge" or "common sense" to one of ordinary skill in the art without specific factual findings and some concrete evidence in the record to support these findings will not support an obviousness rejection). Moreover, if the Examiner relies on his or her personal knowledge to supplement what is actually known in the art, the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the supplementation. 37 CFR 1.104(d)(2).

Here, the Examiner provides no such evidence or affidavit supporting the Examiner's apparent taking of official notice for all of Examiner's rejections and the Examiner's assertion that Applicant's development would have been obvious to one skilled in the art. In response to this paper, Applicant respectfully requests such evidence or affidavit according to rule 37 CFR 1.104(d)(2).

Note, as a first example, the optimization of the particular variables here has not been shown, and is supplemented by the Examiner's supposition to this effect. As another example, the Examiner's statement that "Cassel does not explicitly teach a composition comprising a combination of lidocaine, prilocaine and tetracaine" (Office Action, page 6, final para.) is one such basis for the Examiner's supplementation. Another such notation is that "the references do not explicitly teach the claimed amounts of anaesthetic agents or methyl pyrrolidone" but that one skilled in the art "would have been motivated to optimize the amounts of the herein claimed

anaesthetics." (Office Action, page 7, para. 2.) The Examiner has failed to provide any affidavit or other evidentiary support for the assertion that it would be obvious to use a combination of lidocaine, prilocaine and tetracaine, and to experiment to combine them in the amounts taught by Applicant. This is the case with each of the Examiner's rejections, and Applicant respectfully requests the above-mentioned affidavit as a basis for rejections on these grounds.

All of the obviousness rejections are thus obviated and/or traversed and can be withdrawn. Action to this end is respectfully requested.

CONCLUSION

Applicant notes that all rejections are obviated or traversed and respectfully requests that they thus be withdrawn. A timely Notice of Allowance is thus requested to be issued in this case. Applicant believes no fees or petitions are due with this filing. However, should any such fees or petitions be required, please consider this a request therefore and authorization to charge Deposit Account No. 02-2093 as necessary.

Dated: July 16, 2008.

Respectfully submitted,

/peterbscull/

Peter B. Scull, Registration No. 37,932
Attorney for Applicant
USPTO Customer No. 43,439

BERENBAUM, WEINSHIENK & EASON, P.C.
370 Seventeenth Street, Suite 4800
Denver, Colorado 80202
Tel: 303-592-8378
Fax: 303-629-7610